Comparison of Glucosamine-Chondroitin Sulfate with and without Methylsulfonylmethane in Grade I-II Knee Osteoarthritis: A Double Blind Randomized Controlled Trial

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ABSTRAK

Latar belakang: *glukosamin-kondroitin sulfate sering digunakan untuk mencegah degenerasi lutut lebih lanjut pada osteoartritis (OA). Metilsulfonilmetan (MSM) adalah suplemen yang mengandung belerang organik dan juga dilaporkan memperlambat progresifitas kerusakan anatomis pada OA lutut. MSM sering dikombinasikan dengan glukosamin dan kondroitin sulfat. Namun, masih terdapat kontroversi apakah glucosamin-kondroitin sulfat atau kombinasinya dengan methylsulfonylmethane secara efektif dapat mengurangi rasa sakit pada OA. Penelitian ini bertujuan membandingkan perbaikan klinis glukosamin-kondroitin sulfat (GK), glukosamin-kondroitin sulfat-metilsulfonilmetan (MSM) (GKM) dan plasebo pada pasien osteoartritis derajat Kellgren-Lawrence I dan II.* ***Metode:*** *suatu uji klinis acak tersamar ganda dilakukan pada 147 pasien dengan OA lutut derajat Kellgren-Lawrence I atau II. Subyek dibagi menjadi 3 kelompok, dengan metode randomisasi blok permutasi, yaitu kelompok GK (n=49), GKM (n=50) dan plasebo (n=48). Kelompok GK mendapat 1500 mg glukosamin + 1200 mg kondroitin sulfat + 500 mg sakarumlaktis; kelompok GKM mendapat 1500 mg glukosamin + 1200 mg kondroitin sulfat + 500 mg MSM; kelompok plasebo menerima 3 kapsul yang serupa berisi sakarum laktis. Obat-obatan ini diberikan sekali sehari selama 3 bulan berturut-turut. Skor VAS dan WOMAC dinilai sebelum pemberian terapi, kemudian pada minggu ke 4, 8 dan 12.* ***Hasil:*** *pada analisa statistik ditemukan perbedaan signifikan pada minggu ke 12, dimana kelompok GK pada skor WOMAC berbeda signifikan dibandingkan dengan GKM dan plasebo (p=0,005), sedangkan GKM pada skor VAS berbeda signifikan dibandingkan dengan GK dan plasebo (p=0,001). Pada analisis lebih lanjut ditemukan bahwa terdapat perbedaan signifikan pada kelompok GKM dan GM pada skor VAS. Efektivitas pemberian per 4 minggunya ditemukan berbeda bermakna pada kelompok GKM dan plasebo (p<0,005).* ***Kesimpulan:*** *kombinasi glukosamin-kondroitin sulfat-metilsulonilmetan menunjukkan manfaat klinis yang lebih baik untuk pasien OA sendi lutut Kellgren-Lawrence derajat I dan II dibandingkan dengan GK dan plasebo. Sedangkan suplemen GK secara umum tidak menunjukkan manfaat klinis yang lebih baik pada pasien OA sendi lutut derajat Kellgren Lawrence I-II.*

Kata kunci: *glukosamin, kondroitin sulfat, metilsulfonilmetan, osteoartritis.*

ABSTRACT

Background: *Glucosamine, chondroitinsulfate are frequently used to prevent further joint degeneration in osteoarthritis (OA). Methylsulfonylmethane (MSM) is a supplement containing organic sulphur and also reported to slow anatomical joint progressivity in the knee OA. The MSM is often combined with glucosamine and chondroitin sulfate. However, there are controversies whether glucosamine-chondroitin sulfate or their combination with methylsulfonylmethane could effectively reduce pain in OA. This study is aimed to compare clinical outcome of glucosamine-chondroitin sulfate (GC), glucosamine-chondroitin sulfate-methylsulfonylmethane (GCM), and placebo in patients with knee osteoarthritis (OA) Kellgren-Lawrence grade I-II.* ***Methods:*** *a double blind, randomized controlled clinical trial was conducted on 147 patients with knee OA Kellgren-Lawrence grade I-II. Patients were allocated by permuted block randomization into three groups: GC (n=49), GCM (n=50), or placebo (n=48) groups. GC group received 1500 mg of glucosamine + 1200 mg of chondroitin sulfate + 500 mg of saccharumlactis; GCM group received 1500 mg of glucosamine + 1200 mg of chondroitin sulfate + 500 mg of MSM; while placebo group received three matching capsules of saccharumlactis. The drugs were administered once daily for 3 consecutive months VAS and WOMAC scores were measured before treatment, then at 4th, 8th and 12th week after treatment.* ***Results:*** *on statistical analysis it was found that at the 12th week, there are significant difference between three treatment groups on the WOMAC score (p=0.03) and on the VAS score (p=0.004). When analyzed between weeks, GCM treatment group was found statistically significant on WOMAC score (p=0.01) and VAS score (p<0.001). Comparing the score difference between weeks, WOMAC score analysis showed significant difference between GC, GCM, and placebo in week 4 (p=0.049) and week 12 (p=0.01). In addition, VAS score also showed significant difference between groups in week 8 (p=0.006) and week 12 (p<0.001).* ***Conclusion:*** *combination of glucosamine-chondroitinsulfate-methylsulfonylmethane showed clinical benefit for patients with knee OA Kellgren-Lawrence grade I-II compared with GC and placebo. GC did not make clinical improvement in overall groups of patients with knee OA Kellgren Lawrence grade I-II.*

Keywords: *Glucosamine, chondroitin sulfate, methylsufonylmethane, osteoarthritis.*

INTRODUCTION

Osteoarthritis (OA) is one of the most common degenerative joint disorders in the knee which prevalence increases dramatically along with the rise of life expectancy. Many studies were performed to obtain effective and safe regimens to prevent or even reverse the degenerative process in osteoarthritis. Progressive destruction of articular cartilage can result in swelling, pain, and disability.[1,2]

Common drugs for OA treatment are analgetics and non-steroidal anti-inflammatory drugs (NSAIDs) which have a long term side effects. Therefore, there is still an unmet need for alternative therapies for OA which are efficacious and well-tolerated. Combinations of glucosamine-chondroitin sulfate (GC) or glucosamine-chondroitinsulfate-methylsulfonylmethane (MSM) (GCM) are considered as food supplements according to Food and Drug Administration (FDA). Although many controversies arise about the use, it is still commonly used in daily clinical practice.[2,3]

Glucosamine, chondroitinsulfate are frequently used to prevent further joint degeneration in OA. Methylsulfonylmethane (MSM) is a supplement containing organic sulphur and also reported to slow anatomical joint progressivity in the knee OA. The MSM is often combined with glucosamine and chondroitin sulfate. However, there are controversies whether glucosamine-chondroitin sulfate or their combination with methylsulfonylmethane could effectively reduce pain in OA.[3-5] This study compared clinical outcome of glucosamine-chondroitine sulfate (GC) and glucosamine-chondroitine sulfate-MSM (GCM) treatment based on WOMAC and VAS score assessment in patients with first and second grade of (Kellgren-Lawrence) knee OA.

METHODS

This was a double blind randomized controlled clinical trial on 147 patients with

first and second grade (Kellgren-Lawrence) of knee OA. The diagnosis of knee osteoarthritis was based on clinical examination and X-ray imaging. Grading of the disease was done using antero-posterior knee X-ray and determined by using Kellgren Lawrence grading score. Eligibility criteria was symptomatic knee OA according to American College of Rheumatology (ACR)[6] for at least 6 months, confirmed and grading by radiographic imaging according to Kellgren Lawrence score.[7] Exclusion criteria were patients with inflammatory arthritis and other types of arthritis, patients with diabetes mellitus, patients who have history of recent knee injury, patients who lack of ability to perform or comply with treatment procedure.

Subjects were allocated by permuted block randomization into three groups, glucosamine-chondroitinsulfate (GC; n=49), glucosamine-chondroitin sulfate-MSM (GCM; n=48), and placebo (n=50); and sampling was done consecutively. The GC group received 1500 mg of glucosamine + 1200 mg of chondroitin sulfate + 500 mg of saccharumlactis; GCM group received 1500 mg of glucosamine + 1200 mg of chondroitin sulfate + 500 mg of MSM; while placebo group received three matching capsules of saccharum lactis. These drugs were administered once daily for three consecutive months. Treatment outcome was measured by Western Ontario and McMaster University Osteoarthritis Index (WOMAC)[8] andVisual Analog Scale (VAS)[9] scores.WOMAC score is questionnaire to assess pain, stiffness and physical function in OA patients. Evaluation was done at the baseline, then at the 4th, 8th, and 12th week after treatment.

The distribution of WOMAC and VAS groups at 4th, 8th, and 12th week was analyzed using one-sample Kolmogorov-Smirnov test using SPSS. For groups with normal distribution, ANOVA test was performed to compare with the baseline, followed by posthoc Bonferonni test for subgroup analysis. For groups with abnormal data distribution, Kruskall-Wallis test were performed, followed by Mann-Whitney test for subgroup analysis. Independent t-test were also used to analyse the mean and median difference between GCM and GC groups for each week. Additionally, the data distribution of GCM, GC, and placebo group at the 4th, 8th, and 12th week were analysed. Afterward, paired t-test test were

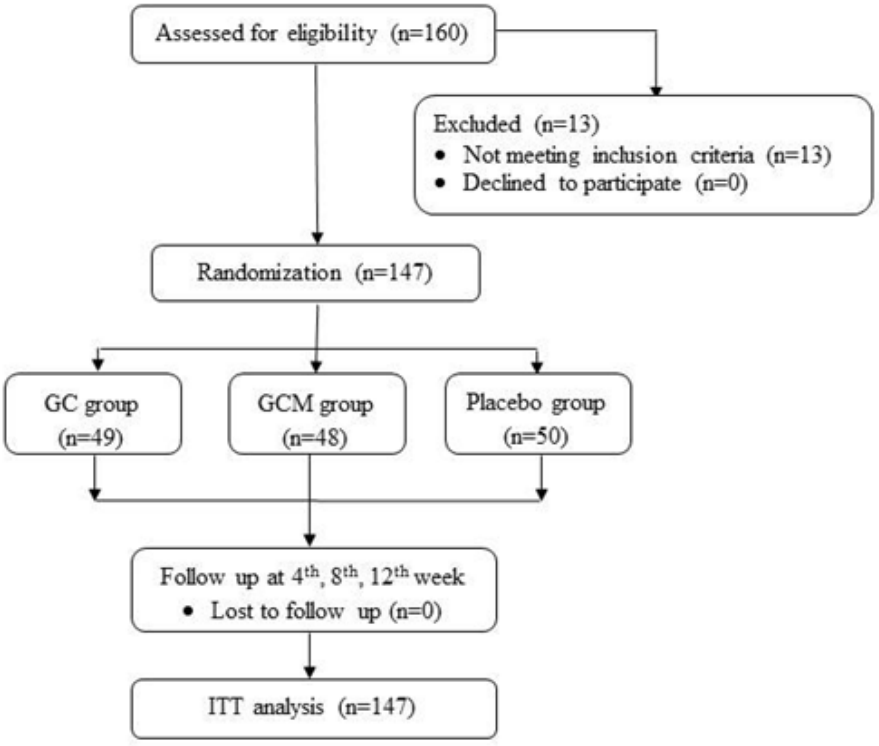

Figure 1. Subject flowchart

performed to compare the normally distributed groups with the baseline based on WOMAC and VAS scores, while Wilcoxon test were performed at the abnormally distributed groups.The p-value less than 0.05 were considered as significant.

The study adheres to the guidelines of the ethical review process issued by the Health Research Ethical Committee of FKUI/RSCM. Ethical clearance has been issued for the study in February 2013(78/H2.F1/ETIK/2013).

RESULTS

A total of 160 patients were screened and 13 patients were excluded (5 patients were diagnosed rheumatoid arthritis, 3 patients had history of traumatic knee injury, 2 patients had diabetes mellitus, and 3 patients could not comply with the treatment and evaluation procedures). Thus, 147 patients were eligible for this study and underwent randomization (**Figure 1**). From 147 patients, the mean age of patients was 61 years, and 67.3% of them were woman. Baseline VAS score were roughly similar between the GCM (4 SD 1.6), GC (3.8 SD 1.6), and placebo group (3.54 SD 1.5). Baseline WOMAC score was equal in the GCM (34.16 SD 15.9) and placebo (34.65 SD 7.5) groups, but it was slightly lower in the GC group (27.73 SD 9.3). This difference was not statistically significant (p>0.05). There was a slight predominance of female prevalence in the male to female ratio (1:2) from the samples. There was also no significant difference between the number of patients with unilateral and bilateral knee OA and also the number of patients with first grade and second grade of knee OA among those three groups (**Table 1**).

Table 1. Baseline characteristics of patients

	GCM (n=50)	GC (n=49)	Placebo (n=48)
Mean of age (years)	58.3 (10.4)	60.9 (9.3)	62.8 (7.5)
Gender (%)			
- Male	22	34.7	58.3
- Female	78	65.3	41.7
WOMAC, mean (SD)	34.16 (15.9)	27.73 (9.3)	34.65 (14.65)
VAS, mean (SD)	4.04 (1.6)	3.82 (1.6)	3.54 (1.5)
Osteoarthritis (%)			
- Unilateral	12.5	10.2	14
- Bilateral	87.5	89.8	86
- Grade 1	54	63.3	41.7
- Grade 2	46	26.7	58.3

Table 2 presented the result of between groups analysis, either between weeks or between treatment groups. At the 12th week, there was significant difference between three treatment groups on the WOMAC score (p=0.03) and on the VAS score (p=0.004). When analyzed between weeks, GCM treatment group was found statistically significant on WOMAC score (p=0.01) and VAS score (p<0.001).

On further subgroup analysis, GC treatment group was found statistically significant at the 12th week compared to placebo group (p=0.005). While on the 12th week, GCM treatment group

Table 2. Statistical analysis of WOMAC and VAS score

WOMAC	GC	GCM	Placebo	P-value
Week 0	27.73 (SD 17.08)	34.16 (SD 15.98)	34.65 (SD 14.65)	0.06[a]
Week 4	25.38 (SD 15.99)	29.04 (SD 16.09)	29.06 (SD 15.15)	0.41[a]
Week 8	24.43 (SD 15.97)	27.04 (SD 14.68)	28.85 (SD 13.98)	0.35[a]
Week 12	21.02 (SD 13.15)	22.04 (SD 11.34)	29.19 (SD 13.15)	0.03*[a]
P-value	0.12[a]	0.01*[a]	0.168[a]	
VAS	**GC**	**GCM**	**Placebo**	**P-value**
Week 0	4.00 (1.00-8.00)	4.00 (2.00-9.00)	3.00 (0.00-7.00)	0.539[k]
Week 4	3.00 (0.00-10.00)	3.00(1.00-8.00)	3.00 (1.00-7.00)	0.898[k]
Week 8	3.00(1.00-8.00)	3.00(1.00-9.00)	3.00 (1.00-6.00)	0.100[k]
Week 12	3.00 (1.00-6.00)	3.00 (1.00-6.00)	3.00 (1.00-6.00)	0.004*[k]
P-value	0.598[a]	<0.001*[a]	0.855[a]	

*significant p<0.05; [a)] ANOVA test; [k)] Kruskall Wallis test

Table 3. Statistical analysis of WOMAC and VAS score difference with week 0

WOMAC	GC	GCM	Placebo	P
Week 0	-	-	-	-
Week 4	0.00 (-33 – 26)	-4.50 (-30 – 35)	-3.50 (-39 – 27)	0.049*[k]
Week 8	-3.74 (SD 13.17)	-7.12 (SD 10.85)	-5.79 (SD 11.44)	0.372[a]
Week 12	-4.00 (-53 – 16)	-13.50 (-53 – 13)	-1.00 (-41 – 23)	0.01*[k]
VAS	**GC**	**GCM**	**Placebo**	**P**
Week 0	-	-	-	-
Week 4	0.00 (-4.00 – 3.00)	0.00 (-3.00 – 2.00)	0.00 (-3.00 – 4.00)	0.368[k]
Week 8	0.00 (-3.00 – 3.00)	-1.00 (-4.00 – 3.00)	0.00 (-2.00 – 4.00)	0.006*[k]
Week 12	0.00 (-4.00 – 2.00)	-1.00 (-5.00 – 1.00)	0.00 (-3.00 – 4.00)	<0.001*[k]

*significant p<0.05; [a)] ANOVA test; [k)] Kruskall Wallis test

was found significant compared to week 0 (p<0.001). On the other hand, analysis of VAS score based on week of observation, at week 12 GCM showed a significant difference compared to placebo group (p=0.001). Within GCM group itself, there was significant difference in week 12 compared to week 0 (p<0.001).

Turning to score difference (**Table 3**), comparison of WOMAC score analysis showed significant difference between GC, GCM, and placebo in week 4 (p=0.049) and week 12 (p=0.01). In addition, VAS score also showed significant difference between groups in week 8 (p=0.006) and week 12 (p<0.001).

DISCUSSION

Glucosamine, chondroitin sulfate, and MSM are suggested to have an effect in decreasing pain and reducing further joint degradation in knee OA. However, there are debates on their efficacy as combination of glucosamine-chondroitin sulfate or glucosamine-chondroitin sulfate-MSM in osteoarthritis patients. This study was aimed to evaluate the efficacy of the combination of glucosamine and chondroitinsulfate with and without combination with MSM compared to placebo in grade I and II (Kellgren-Lawrence) of knee OA patients.

Baseline characteristic showed a slightly lower WOMAC score in the GC group, although it was not statistically significant; thus, it might present bias in the comparison of WOMAC score to other group. This difference was probably due to a slightly higher number of first degree knee OA patients in this group.

Generally, WOMAC scores at the 4th, 8th, and 12th week improved in all three groups. However, the significant scores was observed only at week 12 when compared to baseline. Comparing between the groups, GCM treatment groups showed significant on WOMAC score changes compared to placebo.Within group analysis also support the advantage of GCM on the 12th week on both scores. The sulfur contained in the MSM might also play role in replacing the loss of sulfur in the connective tissue during arthritis process.[3-5] In OA, glucosamine, chondroitin sulfate, and MSM work slower,[4,5] so that the difference of WOMAC and VAS score was more obvious in both interference groups at week 12.

However, the result of its WOMAC score in this study was not in line with GAIT study reporting that there was no significant difference of WOMAC pain and WOMAC function scores in knee OA patient compared to placebo.[10] Messier, et al.[11] evaluated the efficacy of a daily dose of glucosamine 1500 mg and chondroitin sulfate 1200 mg with physical exercise compared to placebo with physical exercise in the physical function of 89 patients with knee OA for 12 months. This study did not find any difference in the function, mobility, and pain between control and the treatment group even though they added 6 months period of treatment follow up. This significant decrease was possibly due to the baseline score difference in the GC group compared to placebo.[12-15]

Turning to pain perception, in our study the VAS score evaluation at week 4, 8, and 12 were also decreased in all three groups; however, the difference was also only statistically significant at week 12 in the GCM group compared to the placebo group, but not in the GC group. The significant decrease of VAS score in the GCM group might be related to the analgetic effect of MSM, and hence it has the ability to reduce pain.[4,5] This finding was also in accordance with the previous research where GC worked slowly on the cartilage joint and hence the effect could only be observed at least 9 weeks after treatment.[16,17] This result was similar with previous study and strengthening the role of analgetic effect of MSM in decreasing VAS score.[18,19]

The decrease of VAS score at week 12 in the placebo group was comparable to that in the GC group. This finding was similar to the result of GAIT study stating that there was no difference of VAS score between GC and placebo group.[10] Similar result was also reported by Messier, et al.[11] although they have added 12 months of muscle exercise to get greater difference in function, mobility, and pain scores between placebo and GC group. The lack of treatment effect of GC might be due to the fact that the majority of oral chondroitin sulfate could not be hydrolyzed into monosaccharide in the digestive tract, and the fact that only a small amount of di-, oligo-, and polysaccharide are able to pass through the digestive process in the gut and absorbed to the blood. Due to this hydrolysis process, oral absorption of chondroitin was zero percent for high molecular weight chondroitinsulfate and 8-12% for lower molecular weight chondroitin sulfate with more sulfate ratio. Apart from its size, chondroitin administered orally is only partially absorbed by the gut, hence only little amount of it may reach the joint.[12-15] Our findings indicate that glucosamine-chondroitin sulfate was not effective in reducing joint pain in OA compared to placebo. Thus, this result should be considered when clinicians would like to recommend supplement containing glucosamine-chondroitin sulfate to their OA patients.

CONCLUSION

Combination of glucosamine-chondroitin sulfate-MSM showed a significant clinical improvement especially in terms of pain relief in patients with grade I-II Kellgren Lawrence of knee osteoarthritis (OA) compared with glucosamine-chondroitin sulfate and placebo. Glucosamine-chondroitin sulfate may bring significant clinical improvement in patients with grade I-II Kellgren Lawrence of knee OA compared to placebo; however, the supplement could not significantly reduce pain.

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